

REMARKS

Upon entry of the present amendment, claims 2, 3, 5-14, 16-17, and 19-37 are canceled, claims 1, 15, and 18 are amended. Accordingly, claims 1, 4, 15, 18, and 38-40 are presently pending.

At the outset, Applicants wish to thank Examiners Rooney and Haddad for taking the time to meet with Applicants' representative to discuss the pending rejections and Applicants' proposed response. Applicants submit that the instant remarks not only address the grounds of rejection set forth in the outstanding Final Rejection of March 11, 2008 but also the concerns raised by the Examiners in the course of the interview of June 3, 2008 and suggestions set forth therein. In particular, in an effort to expedite prosecution and further distinguish the claimed invention from the disclosures of the cited prior art, Applicants have herewith restricted independent claim 1 to an isolated allergen consisting of a polypeptide capable of binding to IgE antibodies from an individual being allergic against mugwort pollen selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1; (b) a polypeptide comprising the amino acid sequence extending between residues 21 and 180 of SEQ ID NO:1; and (c) a polypeptide comprising the amino acid extending between residues 181 and 396 of SEQ ID NO:1. Applicants respectfully submit that the allergen of the present claims, as well as the pharmaceutical composition and diagnostic kit associated therewith, are not only described and enabled by the instant specification but further novel and non-obvious over the prior art of record. Applicants further submit that no new matter has been added. However, Applicants reiterate that this amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Pursuant to the Final Office Action of March 11, 2008, elected claims 1, 3-4, 15, 18, 20, and 38-40 stand rejected on both reference and non-reference grounds. To expedite prosecution, Applicants have canceled claims 3 and 20, leaving only claims 1, 4, 15, 18, and 38-40 at issue. Applicants respectfully submit that the instant response renders moot the outstanding claim rejections and places the instant application in condition for allowance. Further to this position, Applicants submit the following remarks:

Rejections Under 35 USC 112, First Paragraph

Enablement:

The Examiner maintained and made final the rejection of claims 1, 3-4, 15, 18, 20, and 38-40 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

With respect to claims 1 *et seq.*, while the Examiner finds the specification to be enabling for an allergen consisting of SEQ ID NO:1, consisting of amino acids 181-to 396 of SEQ ID NO: 1, and consisting of amino acids 21 to 180 of SEQ ID NO:1, and compositions and kits thereof, she finds it does not reasonably provide enablement for polypeptides comprising such sequences. The Examiner asserts that use of the open-ended term “comprising” broadens the claim to encompass any number of undisclosed amino acids added onto the N- and/or C-terminus of the polypeptide of SEQ ID NO:1. According to the Examiner, such undisclosed amino acids may function to treat allergies independent of the SEQ ID NO: 1.

At the outset, Applicants wish to point out that claims 38-40 are indeed limited to an allergen consisting of SEQ ID NO:1, consisting of amino acids 181-to 396 of SEQ ID NO: 1, and consisting of amino acids 21 to 180 of SEQ ID NO:1, respectively. Accordingly, it is unclear why these claims are included in the instant enablement rejection. Clarification is requested.

As for the remaining claims (i.e., claims 1, 4, 15, and 18), the Examiner suggests that without express guidance as to which “core structures of SEQ ID NO:1 are essential for IgE binding”, which “amino acids can be added that also might bind IgE” and which “regions [are] critical for activity”, the experimentation left to those skilled in the art is undue. Applicants respectfully disagree.

The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. For an Examiner to sustain a rejection on the grounds of enablement, she must provide evidence that the claimed method could not be performed without undue experimentation, bearing in mind that the test for undue experimentation is not merely quantitative. In fact, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect

to the direction in which the experimentation should proceed. The factors to be considered when determining whether the specification is enabled and whether any necessary experimentation is “undue” include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention.

In this case, the instant specification clearly contemplates compositions comprising the allergenic sequence of the present invention in combination with other useful sequences. For example, at p. 8, lines 7-11 and p. 9, lines 24-31, Applicants expressly describe the inclusion of amino acid sequences which facilitate isolation and/or purification of the polypeptide of interest upon expression in a host cell, examples of which include a “6XHis tag, a FLAG tag, and sequences encoding bacterial proteins such as GST.” Applicants respectfully submit that the manufacture of such heterologous fusion proteins is routine in the art of recombinant proteins. The present invention also contemplates pharmaceutical compositions comprised of the inventive allergens in combination with other therapeutically useful peptides, such as other allergenic peptides, synthetic epitopes, and adjuvants (see p. 11, line 29, to p. 12, line 10). Given the high level of skill in the art and the fact that a vast number of adjuvant and fusion constructs are presently known, and indeed conventional, in the art of peptide-based immunotherapy, the “trial and error” testing needed to identify suitable N-terminal or C-terminal additions is within the parameters of routine experimentation and optimization.

Furthermore, while it is well settled that the presence of some potentially inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)), Applicants respectfully submit that such potentially inoperative embodiments are excluded by the current claim language which requires that the allergen at issue bind to IgE antibodies from an individual being allergic against mugwort pollen, a function that is readily and routinely assayable using conventional techniques. See, for example, p. 4, lines 23-28. Thus, in that a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art, Applicants submit that one of ordinary skill in the art would be able to

practice the invention of the presently pending claims without undue experimentation with a reasonable expectation of success.

With respect to claim 18, the Examiner continues to challenge the enablement of a kit for the “*prevention*” of an allergic disorder. While Applicants maintain that the Examiner’s interpretation of the term “prevention” in the context of the present invention is unduly restrictive, Applicants have nevertheless canceled the term “prevention” from kit claim 18 to expedite prosecution. Thus, in that the present amendment to claim 18 renders moot the enablement rejection thereof, Applicants respectfully request reconsideration and withdrawal of the rejection.

With respect to claim 15, the Examiner continues to challenge the *in vivo* pharmaceutical efficacy of the claimed allergen peptide in the context of treating allergy, noting that allergens by definition bind IgE, thereby giving rise to allergy and anaphylaxis. The Examiner thus concludes that there is no reasonable correlation between a polypeptide that binds to IgE and an *in vivo* treatment method for allergies. Applicants respectfully disagree.

As noted on page 1 of the instant specification, it is nowadays widely accepted that recombinant allergens represent promising tools for diagnosis and therapy for Type I allergy. Peptide-based hypersensitization immunotherapy, whereby peptide agents bind cellular components of the immune system so as to suppress or desensitize the allergic response to particular allergens, is the gold standard for allergy treatment. Accordingly, allergen preparations are routinely made and administered for therapeutic purposes (e.g., to modify the allergic response of an allergen sensitive individual to a particular allergen). Purified allergen polypeptides and modified versions thereof may, for example, modify the B-cell response to an allergen, the T-cell response to an allergen or a combination of both. Purified allergens can also be used to design modified derivatives or analogues which are more useful in immunotherapy than are the unmodified, naturally-occurring peptides, such modified derivatives or analogues having the same or enhanced therapeutic properties with reduced side effects, especially reduced anaphylactic reactions. Accordingly, given the advanced state of the art of allergy therapy, Applicants respectfully submit that the *in vitro* data presented herein, data that demonstrates that

the inventive polypeptides show clear and specific binding to mugwort pollen specific IgE antibodies, is sufficient to establish its utility in the context of allergy therapy.

Nevertheless, in an effort to expedite prosecution, Applicants submit herewith a declaration from Dr. Fatima Ferreira, including experimental data (Appendix A) that further confirms the pharmaceutical utility of the presently claimed allergens.

Numerous publications have shown that successful immunotherapy of allergic patients correlates with the modulation of allergen-specific T cells. Accordingly, a composition designed for allergen-specific immunotherapy should be able to address the existing T cells specific for the particular allergen to which the patient is allergic. These aspects are discussed in the review article by Larch et al. provided herewith as Appendix C (Larche, M. et al., "Immunological Mechanisms of Allergen-Specific Immunotherapy", *Immunology*, Vol. 6: 761-771, October 2006). As noted therein, in order to be successful, the allergy therapy should target the same T cell population that causes the development of the allergic reaction. However, through the inclusion of therapeutic adjuvants, these existing T cells will receive a "non-allergic" signal and will drive the immune response to the allergen in a "non-allergic" direction. This means the synthesis of IgE antibodies will decrease and the IgG will increase, both due to different cytokines secreted by the T cells.

The stimulation index (SI) reflects the ability of an allergen or a peptide fragment thereof to activate T cells to proliferate. The SI is high when the allergen or peptide is added to the T cell culture and it is low when there is no allergen or peptide added. In order to distinguish background T cell proliferation from proliferation specifically induced by a peptide or by the intact allergen, Applicants set up a threshold value of 5. This means a reaction is considered positive (proliferation in response to the allergen) when the measured values of incorporated radioactivity is at least 5 times higher than the values in the T cell cultures without allergen/peptide added to the culture medium. As the data presented in the declaration provided herewith clearly demonstrate, the stimulation of peripheral blood mononuclear cells obtained from ragweed allergic individuals with the recombinant mugwort pollen allergen of the present invention (i.e., Art v 6 of SEQ ID NO: 1) induces proliferation of T cell lines at optimum concentrations (i.e., SI 4.3 to 11.2) as compared to that of non-allergic individuals (i.e., SI 1.5 to 4.2) and, as such, would be expected to have therapeutic utility in the context of allergen-specific immunotherapy.

Thus, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification as well as the attached declaration demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the presently pending claims without undue experimentation with a reasonable expectation of success. Therefore, Applicants respectfully request reconsideration and withdrawal of the enablement rejection of claim 15 in view of the amendments and remarks herein.

Written Description:

The Examiner maintained and made final the rejection of claims 1, 3-4, 15, 18, 20, and 38-40 under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to reasonably convey possession of the claimed invention. While the Examiner accedes to Applicants' possession of an allergen consisting of SEQ ID NO:1, consisting of amino acids 181-to 396 of SEQ ID NO: 1, and consisting of amino acids 21 to 180 of SEQ ID NO:1, and compositions and kits thereof, she continues to challenge Applicants' possession of the genus of allergens comprising such sequences. According to the Examiner, the limited examples are insufficient to represent the degree of diversity encompassed by the claimed genus.

As above, Applicants wish to point out that claims 38-40 are indeed limited to an allergen consisting of SEQ ID NO:1, consisting of amino acids 181-to 396 of SEQ ID NO: 1, and consisting of amino acids 21 to 180 of SEQ ID NO:1, respectively. Accordingly, it is unclear why they are included in the instant written description rejection. Clarification is requested.

As for the remaining claims (namely, presently pending claims 1, 4, 15, and 18), as noted previously, the standard for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). The standard for determining sufficiency of the description is "factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In re Wertheim*, 541 F.2d at 262 (citing *In re Ruschig* 379 F.2d 990, 995-96 (C.C.P.A. 1967)). It is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without

describing all species that the claim encompasses. The law does not require that the specification describe the exact details for preparing each and every species within the genus described. In fact, even if the Examiner considers the subject matter of the claims to be broader than that disclosed in the original specification, the written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the earlier specification.

In this case, Applicants respectfully disagree with the Examiner's position and submit her conclusions are in conflict with the recently promulgated Revision 1 of the Written Description Training Materials published March 25, 2008 (www.uspto.gov/web/menu/written.pdf), particularly Examples 4 and 15, both of which validate the use of open-language in this context. In assessing adequacy of written description, the examples expressly conclude that it is within the level of skill and knowledge in the art to add any desired DNA sequence to either end of a particular sequence, with no more than routine experimentation. Because the claimed sequence is a structural feature common to members of the claimed genus and the specification describes the complete structure (sequence) of the molecule, one skilled in the art would recognize that the applicant was in possession of a structural feature shared by members of the claimed genus. Accordingly, the species disclosed in the specification; *i.e.*, SEQ ID NO: 1 and the functional fragments thereof, are sufficiently representative of the claimed genus and thus the written description requirement of 35 U.S.C. 112, first paragraph, is satisfied.

Thus, Applicants respectfully submit that the instant specification provides an adequate written description of the genus of allergens encompassed by claims 1 *et seq.*, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection of claims 1, 3, 4, 15, 18, 20, and 38-40 in view of the amendments and remarks herein.

Rejections Under 35 USC 102

The Examiner maintained and made final the rejections of claims 1, 3-4, 15, 18, 20, and 38 under 35 U.S.C. § 102(b) for being anticipated by one or more of Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., and Paulsen et al. According to the Examiner, the prior art references disclose "an approximately 44 kDa polypeptide allergen in mugwort

pollen that appears to be identical to Applicants' "Art v 6" protein (SEQ ID NO: 1). The Examiner continues to assert that the claimed structural and functional characteristics are inherently taught by the prior art disclosures. Accordingly, the Examiner finds the prior art references disclose or suggest and therefore anticipate the invention of claims 1, 3-4, 15, 18, 20, and 38.

Applicants not only disagree with the Examiner's characterization of the prior art disclosures but also submit that the Examiner has erroneously placed the burden on Applicants to "prove" that the claimed allergen is distinct from the peptide of the prior art. Applicants reiterate that it is not their burden to demonstrate uniqueness but instead the Examiner's burden to demonstrate anticipation. Thus, it is improper to demand that Applicants "prove" that the various "approximately 40.9 kDa" mugwort pollen extracts of the prior art are different from that which is presently claimed, particularly when Applicants have previously presented ample evidence suggestive of distinction (e.g. differences in measurable parameters such as MW, pI, amino acid composition, etc.) and more recently accumulated evidence that casts doubt on the Examiner's suggestion that Applicants' SEQ ID NO:1 is "more likely than not" to be among the mugwort pollen extracts identified in the prior art (see Appendix B of the attached declaration). Specifically, as the data provided herewith as Appendix B demonstrates, several potentially allergenic proteins within the range of 40-44 kDa band coexist in mugwort pollen extract.

As noted previously, the suggestion that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Likewise, the fact that an event *may* result from a given set of circumstances is not sufficient to establish anticipation. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Under the principle of inherency, anticipation may not be established by probabilities or possibilities ("A prior art event cannot be established based on speculation, or where a doubt exists." *Ethyl Molded Product Co. v. Betts Package, Inc.*, 9 USPQ 2d 1001, 1032-33 (E.D.KY 1988)). Rather, the doctrine of inherency is available only when the prior inherent event can be established with certainty. Thus, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Accordingly, when relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably

support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

In this case, Applicants previously presented evidence that the “approximately 44 kDa polypeptide allergens isolated from mugwort pollen using SDS-PAGE gel” allegedly described by Nilsen et al., Brandys et al., Hirschwehr et al., de la Hoz et al., Katial et al. or Paulsen et al. were not identical to the presently claimed polypeptide of SEQ ID NO: 1, referred to in Gen Bank Accession Number AY904433 as “Art v 6”. Applicants herewith present further evidence establishing that the reference proteins could be any one of a number of extract proteins (See Appendix B). Thus, Applicants respectfully submit that since one cannot be certain that the claimed peptide is necessarily present in any of the references, the references cannot anticipate the invention of the pending claims.

In sum, Applicants respectfully submit that none of the polypeptides described in the prior art are identical to the presently claimed ~40.9 kDa Art v 6 protein defined in SEQ ID NO: 1. Since the cited prior art references fail to explicitly or inherently suggest each and every claimed element, Applicants submit that they cannot anticipate the invention of the pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the anticipation rejections of claim 1, 4, 15, 18, and 38 in view of the amendments and remarks herein.

Rejections under 35 U.S.C. § 103

The Examiner maintained and made final the rejection of claim 19 [sic – claim 18?] under 35 U.S.C. § 103(a) for being obvious over Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., or Paulsen et al., further in view of USPN 4,459,360. According to the Examiner, US '360 cures the deficiencies of Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., and Paulsen et al. by disclosing a diagnostic kit for mugwort allergy screening. The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art to package the allergens of the prior art in a kit as taught by US '360.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See M.P.E.P. § 2142, 2143.

Applicants respectfully submit that US '360 fails to cure the above-noted deficiencies of the Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., and Paulsen et al., namely the disclosure of an ~40.9 kDa Art v 6 protein defined in SEQ ID NO: 1. Thus, in that the prior art references, alone or in combination, fail to teach or suggest all the claim limitations, Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection of claim 19 in view of the amendments and remarks herein.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **June 11, 2008**. In that the Petition for a Two-Month Extension of Time extends this deadline to on or before **August 11, 2008**, Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: /JULY 25, 2008/

By: /chalin a. smith/

Smith Patent Consulting, LLC
3309 Duke Street
Alexandria, VA 22314
Telephone: (703) 549-7691
Facsimile: (703) 549-7692

Name: Chalin A. Smith
Title: Attorney for Applicant
Registration No. 41,569

CUSTOMER NUMBER 31,496